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Changing patterns and trends in systemic fungal infections

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Invasive mycoses are a significant and growing public health problem. Although bloodstream infections with *Candida albicans* may be decreasing in frequency, the number of persons at risk for them continues to grow. Moreover, infections with other *Candida* species, such as *Candida glabrata*, are increasing in incidence. Invasive mould infections in general, and *Aspergillus* infections in particular, are becoming more frequent. Fungal opportunistic infections in persons with AIDS are no longer a major problem in developed countries, but are resulting in significant morbidity and mortality in developing countries with AIDS epidemics. Further studies are needed to define populations at very high risk for fungal opportunistic infections who might benefit from targeted antifungal chemoprophylaxis, which remains the most promising of the potential prevention strategies. This review highlights the changing patterns in risk factors, changes in epidemiology, the impact of changes in medical practice in intensive care and organ transplantation on the incidence of systemic fungal infections, and gives an overview of fungal infections in paediatric patients, patients with haematological malignancy, and the emergence of antifungal resistance.

Keywords: aspergillosis, candidosis, antifungals

Introduction

Over the past few years, major advances in healthcare have led to an unwelcome increase in the number of life-threatening infections due to true pathogenic and opportunistic fungi.[1] These infections are being seen in ever increasing numbers, largely because of the increasing size of the population at risk. This population includes transplant recipients, cancer patients and other individuals receiving immunosuppressive treatment. Among patients undergoing transplants or treatment of malignancies, novel and more intensive regimens have resulted in more profound levels of immunosuppression that are sustained for longer periods. Likewise, the increasing use of invasive monitoring and aggressive therapeutic technologies in intensive care units has resulted in improved survival of individuals with life-threatening illnesses, but has also contributed to an increase in the number of persons at risk for fungal infections. Other developments in medical practice that have led to significant changes in the incidence of fungal infections among the different groups of at-risk patients include the increasing use of azole antifungals for treatment and chemoprophylaxis, and the widespread use of amphotericin B for empirical treatment. Today, invasive fungal infections pose the chief infectious challenge in haematology, oncology and intensive care practice.

Only a few species of fungi (yeasts, moulds, and dimorphic fungi) cause human infections.[1] For many years, fungi were believed to be clinically insignificant but an increased incidence of invasive fungal infections during the past 20 years has created a major challenge for healthcare professionals. Mortality among infected patients is high; many studies have shown the death rate is in excess of 90%.

The most frequently encountered infections are caused by the yeast *Candida albicans* and by species of the filamentous fungus *Aspergillus*. Different species tend to predominate in different centres. Other fungal pathogens that have emerged in recent years include yeast species such as *Candida glabrata, Candida krusei* and *Candida tropicalis*, *Cryptococcus* and *Trichosporon*, filamentous fungi such as *Fusarium, Rhizopus* and *Rhizomucor*, and agents of phaeohyphomycosis.[1] Most of these invasive mould infections are acquired through the respiratory tract, whereas *Candida* and perhaps *Trichosporon* infections are usually preceded by harmless colonization of the gastrointestinal tract, skin and mucosal surfaces.

The emergence of these organisms as significant pathogens has important implications for diagnosis and management, not only because the clinical presentation can mimic more common diseases but also because many of the organisms are usually resistant to amphotericin B.

Changing patterns in risk factors

Immunosuppression and breakdown of anatomical barriers such as the skin are the major risk factors for fungal infections.[2,3] Healthcare workers encounter at-risk patients in various settings,

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including AIDS clinics and intensive care, transplantation and oncology units. Patients with prolonged and deep neutropenia (haematological malignancy patients) are most at risk and are therefore most likely to receive prophylactic therapy. The ability to target and neutralize macrophage inflammatory cytokines, particularly tumour necrosis factor-α, has emerged in recent years as one of the most important advances in the treatment of rheumatoid arthritis, Crohn's disease, and several other systemic inflammatory diseases. However, it now apparent that the use of these agents may lead to an increased likelihood of opportunistic infections, including those caused by fungi.

Practical measures can be taken to avoid exposing the patient to fungi, and antifungal agents can be administered to prevent systemic fungal infection. Most fungal infections have non-specific symptoms; this makes recognition of the signs and symptoms of the disease important but also makes diagnosis difficult and empirical treatment necessary. Some antifungal agents have limitations but new formulations will improve therapy and play a key role in future antifungal strategies.

While several epidemiological studies have recently been published addressing risk factors for the common invasive mycoses, no major new preventable or modifiable risk factors have been described.

Invasive candidosis

Risk factors for *Candida* bloodstream infections (BSIs) can be divided into host-related factors, such as immunocompromising conditions, and healthcare-related factors, such as intravascular catheters, broad-spectrum antibiotic use, and surgical procedures. While no new risk factors have emerged in recent studies, *Candida* BSIs remain a serious problem, particularly in neonatal and surgical ICU patients. Several recent studies have helped to further define the risk factors for these infections.[2] Risk factors for *Candida* BSI found in the National Epidemiology of Mycoses Survey (NEMIS) neonatal ICU study included: gestational age less than 32 weeks; 5 min Apgar score less than 5; shock; disseminated intravascular coagulopathy; use of intralipid and parenteral nutrition; central venous catheters, receptor antagonists and proton pump inhibitors; intubation; and length of ICU stay greater than 7 days prior to *Candida* BSI. Independent risk factors identified in the NEMIS surgical ICU study included prior surgery; acute renal failure; and receipt of parenteral nutrition.[2] In addition, triple lumen catheters were associated with increased risk of *Candida* BSIs among patients who underwent surgery. Receipt of an antifungal drug was associated with a significant reduction in risk of *Candida* BSI.

Prior colonization with *Candida* species, particularly of the gastrointestinal tract, is well recognized as a risk factor for *Candida* BSI. In contrast, risk factors for colonization have rarely been studied.[2] The NEMIS study group did, however, examine risk factors for colonization with *Candida* species in their neonatal ICU cohort.[2] When adjusted for length of stay, birth weight and gestational age, use of third-generation cephalosporins, use of central venous catheters, and use of intralipid were associated with *C. albicans* colonization. The latter two factors were also associated with colonization with *C. parapsilosis*, as was use of H2 blockers. Caesarean section was protective for *C. albicans* colonization, suggesting that neonates may become colonized during vaginal delivery. This study also assessed the role of hand colonization among healthcare workers. Of note, hand carriage of *C. parapsilosis* was found among 19% of healthcare workers, leading the authors to suggest that transmission from healthcare workers' hands to neonates is an important mechanism by which *C. parapsilosis* colonization is acquired. Hand carriage rates did not, however, correlate with colonization rates among neonates in the individual neonatal ICUs.

Invasive aspergillosis

Well-established risk factors for invasive aspergillosis include underlying lung disease, prolonged neutropenia, immunosuppressive therapy, corticosteroid therapy, allogeneic haematopoietic stem cell transplantation (HSCT), and graft-versus-host disease (GVHD) and its treatment.[1,2] HSCT recipients more frequently develop disseminated disease, whereas persons with haematological malignancies more commonly develop diffuse invasive pulmonary disease.

One important finding delineating the risk of invasive aspergillosis among recipients of HSCTs has recently been described. The majority of invasive aspergillosis cases among allogeneic transplant recipients occur after engraftment, usually in association with GVHD. In contrast, autologous transplant recipients most frequently develop invasive aspergillosis during the initial period of neutropenia, before engraftment has occurred. This has important implications for devising the most effective strategies to prevent invasive aspergillosis among different groups of transplant recipients, in hospital and community settings.

The high rates of invasive aspergillosis in lung transplant recipients may be a result of a number of factors, including the high prevalence of pre-transplant airway colonization with *Aspergillus* species, the prevalence of cytomegalovirus disease (a known risk factor for invasive aspergillosis) in lung transplant recipients, the immunosuppressive regimens employed, and the fact that the lung allograft is in continuous contact with the external environment.[2,4,5] Among recipients of renal transplants, important risk factors include cadaveric donor, prolonged pre-transplant dialysis, end-stage renal disease due to diabetes, rejection, and maintenance tacrolimus treatment. Of note, as new and more powerful immunosuppressive medications like tacrolimus are developed and become more commonly used, it will be important to assess whether these agents affect the risk of developing invasive fungal infections.

Changes in the epidemiology of systemic fungal infection

Assessing the changing incidence of systemic fungal infections is difficult because many fungal infections are diagnosed only at autopsy. However, the incidence of nosocomially acquired infections clearly has risen in the past two decades, with fungal species now accounting for up to 25% of all hospital-acquired blood infections.[6,7] In particular, *Candida* blood infections have steadily increased since the 1980s and account for 8–15% of all blood infections.[7,8]

The increased incidence of fungal infections has coincided with a decrease in mortality from bacterial infections. This is probably the result of better antibiotic therapy, leading to increased survival of patients who are predisposed to fungal infections, as well as inappropriate antibiotic therapy disrupting the normal microbial flora on the skin and mucosal surfaces.

The spectrum of causal organisms has also changed in recent years. A number of surveys have revealed that more than 75% of *Candida* infections in the 1980s were caused by *C. albicans*[2,7] but recently this proportion has fallen to less than 60%. These changes were further demonstrated in surveys of candidosis episodes in the 1980s and 1990s: *C. albicans* infections decreased from around 90% to 30%, whereas *C. glabrata* infections increased from 2% to 26%, *C. parapsilosis* infections increased from 10% to 20%, and *C. tropicalis* infections increased from 2% to 24%.[2,7]

Invasive aspergillosis is usually caused by *Aspergillus fumigatus* and, to a lesser extent, by *Aspergillus flavus, Aspergillus niger* and *Aspergillus terreus*.[1,9] Recently, an increase in the number of *Aspergillus* infections has been seen, but little information is available on the relative proportions of infections caused by the various *Aspergillus* spp.

Infection by other fungal species is encountered less frequently.[1] *Cryptococcus neoformans* infections occur in 5–10% of HIV-infected patients but are rare in other patient groups. The introduction of more effective triple combination therapies for HIV (so-called highly active antiretroviral therapy; HAART) has reduced the frequency of fungal infections in these patients. However, triple therapy is expensive and *C. neoformans* infection remains a major problem in poorer countries. Endemic systemic fungal infections, which are restricted to certain parts of the world include histoplasmosis, blastomycosis, paracoccidioidomycosis, coccidioidomycosis and penicilliosis, although these are increasingly being reported as opportunistic diseases. Moreover, these endemic mycoses can be a problem as diseases imported by travellers returning to Europe.[10]

Changes in medical practice and impact on the incidence of systemic fungal infections

Changes in medical procedures have contributed to the increased incidence of fungal infections.[1] Normally, anatomical barriers are the first line of defence. The skin and mucosal surfaces stop microorganisms entering the body and are themselves protected by acid pH, enzymes, mucus and other antimicrobial secretions. These barriers are broken down during surgery and when indwelling catheters are used, which allow fungal cells into the body. The number of patients undergoing invasive procedures has increased in recent years. In addition, burns, some viral infections, some bacterial infections, chemotherapy, radiotherapy, and graft-versus-host disease can damage the skin or cause mucosal lesions that allow fungi to reach the tissues and blood.

In healthy individuals, further protection against infection is provided by the immune system. Microorganisms that penetrate the anatomical barriers must overcome four main defence mechanisms: complement, phagocytes, antibodies and cell-mediated immunity. When these systems are compromised or suppressed, the risk of microbial infection increases. Many diseases cause immunodeficiency, the most notorious being AIDS, in which HIV infects and destroys CD4+ T cells. HIV infection weakens the whole immune system and the central role of CD4+ T cells is highlighted by the increased incidence of bacterial, viral and fungal infections in HIV-infected individuals. Patients with other diseases, such as chronic granulomatous disease, have defective neutrophils, phagocytic cells that serve as the first line of defence against fungi. *Candida* and *Aspergillus* spp. are therefore frequently isolated from other patients with chronic granulomatous diseases.

Certain medications can cause immunosuppression. This can be a deliberate strategy, such as when giving immunosuppressive drugs, e.g. corticosteroids to prevent graft-versus-host-disease in allogeneic HSCT recipients or cyclosporin A to prevent or treat rejection in bone marrow transplant (BMT) or solid organ transplant recipients. These immunosuppressive strategies result in lymphopenia, rendering the patient susceptible to viral and mycobacterial infections. Myelosuppressive chemotherapy can also lead to neutropenia in some patients. However, not all neutropenic patients have the same risk of infection. Most patients receiving standard therapy for solid tumours, myeloma or lymphoma have short-lived neutropenia (less than 7 days) and rarely acquire fungal infections but patients with leukaemia who are receiving remission induction therapy are at a higher risk because their neutropenia is often prolonged. Many cancers (such as haematological malignancy) are associated with immunodeficiency and the disease and treatment administered can combine to produce prolonged neutropenia. Deep and prolonged neutropenia (more than 10 days) remains the most important risk factor for fungal infection.

Immunity tends to be weaker in neonates, making them more susceptible to infection.[11] Premature babies, who may also have indwelling catheters or may be receiving broad-spectrum antibiotics, are at a particularly high risk of fungal infection. The increase in survival of premature babies has introduced a new group of at-risk patients.

Nosocomial infections may be acquired from the hospital food or water supply, the hospital environment, and parenteral nutrition.[12,13] Nosocomial *Candida* infections may also be passed to patients by healthcare professionals. This assumption is based on two important findings: (i) a large proportion of medical professionals carry *Candida* on their hands; and (ii) hand washing compliance is as low as 30% among health professionals. Nosocomial outbreaks of aspergillosis can occur when construction or renovation work is being carried out in or near the unit, leading to the contamination of the ventilation system.[12] The source of contamination can also be rooms or units where equipment or medicines are stored or prepared.

Changing practices in intensive care and their impact on candidaemia

Members of the genus *Candida* are the most common fungal pathogens in the ICU setting.[1] They are commensal organisms that normally colonize mucosal and integument surfaces. Although oral and oesophageal infections occur, fungaemia is the most serious clinical syndrome caused by invasive *Candida* infection. However, the importance of the oral cavity as a reservoir of *Candida* must be stressed. Large numbers of yeasts can be found in association with periodontal disease and should be minimized with caution. The manifestations of candidaemia include fever that is unresponsive to antibiotics, and occasionally, it is accompanied by macronodular skin lesions, polymyalgias, or a decline in renal function. A chronic form, chronic disseminated candidosis or so-called 'hepatosplenic candidosis' is also occasionally seen, especially after bone marrow engraftment.

The incidence of systemic candidosis has increased dramatically over the last 50 years, reflecting increasingly interventional standards of medical care.[7] *Candida* species are regularly reported to be the fourth commonest cause of bloodstream infection, and it is perceived that the incidence of systemic candidosis continues to

increase. However, the global disease burden of systemic candidosis is difficult to quantify because of wide geographical variation. Data from the United States indicate that mortality from candidosis has been falling since 1989.[7,14] Data from several locations have reported dramatic increases in candidaemia seen during the 1980s. This experience has either been reported by individual institutions or is country based. For example, a 2 year prospective hospital population-based study of candidaemia has been conducted in the UK. It was carried out on behalf on the British Society for Medical Mycology (BSMM) as part of the European Confederation of Medical Mycology (ECMM) epidemiological survey of candidaemia.[15] Six hospitals in England and Wales acted as sentinel hospitals. Main outcome measures were hospital population-based incidence and 30 day mortality. There were 18.7 episodes of candidaemia per 100 000 finished consultant episodes or 3.0/100 000 bed days and 45.4% cases occurred in ICU patients. *Candida albicans* was isolated in 64.7% of confirmed cases. The majority of isolates were sensitive to standard antifungal agents, including fluconazole. The overall 30 day mortality was 26.4% and removal of the central venous catheter was associated with a significant reduction in mortality. A major conclusion from this study was that the incidence of candidaemia in England and Wales is similar to that in the USA, the majority of isolates remain sensitive to commonly used antifungal agents and mortality associated with this infection appears to be falling.

It appears that the risk of fungal infection is proportional to the length of ICU stay, and many studies have highlighted the need to control for this factor.[16] However, candidaemia itself, for example, prolongs the patient's stay in the hospital, hence the length of stay may be a cause and/or a consequence of infection. This is why 'days prior to the beginning of the first infection' is frequently used to estimate the risk attributable to the length of stay rather than the 'total length of stay'. The most valid alternative for the assessment of the risk per day of exposure to extrinsic risk factors is Cox regression with quantitative time-dependent variables. Cox regression has the advantage of obtaining incidence density ratios, more appropriate for the analysis of the length of stay in the ICU. However, this method implies knowing the exact starting and ending dates of the exposure to a fungal pathogen such as *Candida*, which requires a prospective surveillance system that consumes more resources. However, some centres do use a colonization index to determine risk from *Candida*. Although the distinction between colonization and infection is important, studies in ICU and surgical patients have confirmed that a continuum exists from colonization to infection with *Candida*. Colonization is an independent risk factor for systemic candidosis. It has been has shown, in surgical patients, that routine serial testing for colonization at multiple sites (trachea, urine, skin, stool, surgical wounds and drainage fluids) can be used to define a colonization index (number of positive sites/number of sites tested).[17] A colonization index of greater than 0.5 is associated with an increased risk of deep-seated *Candida* infection.

Candidaemia in paediatric patients

Candida infections have become an increasingly frequent problem in neonatal intensive care units, particularly among extremely low birth weight infants.[11] Transmission occurs both vertically and horizontally, with *C. albicans* and *C. parapsilosis* as the predominant species. Multiple risk factors have been identified with prior antibiotic exposure, presence of a central line, endotracheal intubation, and prior fungal colonization reported most frequently. The primary site of infection can involve the bloodstream, meninges, or urinary tract, but disease is frequently disseminated to multiple organ systems. Amphotericin is the most commonly used antifungal agent, although fluconazole is being used more frequently. The potential role of antifungal prophylaxis is not yet clearly defined, but has been the topic of recent investigative efforts. The crude mortality rate among neonates with systemic candidosis remains ~30%. The following case series is illustrative where a retrospective review of candidaemia episodes in paediatric oncology patients over a 9 year period was conducted.[18] During this period, azole prophylaxis was not routinely used in this group. Thirty-eight episodes of candidaemia were identified: *C. albicans* 29%, *C. tropicalis* 26%, *C. parapsilosis* 24%, *C. krusei* 8%, *C. glabrata* 8%, and *C. lusitaniae* 5%. Species of *Candida* other than *C. albicans* were common in patients not receiving azole prophylaxis. Species typically susceptible to azoles were common among patients not using azoles. Death attributed to the fungal infection occurred in 21% of episodes, with nearly all the deaths occurring in patients with *C. albicans* and *C. tropicalis*. The authors concluded that *C. albicans* is not the predominant species in paediatric oncology patients experiencing candidaemia, even in azole-naive patients.

Fungal infections in patients with haematological malignancy

Systemic fungal infections have become one of the most important causes of infectious disease morbidity and mortality in acute leukaemia patients and after allogeneic stem cell transplantation.[1,19,20] The main risk for fungal infections in patients with acute leukaemia is neutropenia, while allogeneic stem cell transplant patients are vulnerable due to the presence of several different risk factors that include: neutropenia early after the transplant procedure, immunosuppression due to graft-versus-host disease prophylaxis and therapy, the graft-versus-host reaction itself, and other infectious agents (in particular human cytomegalovirus). The practices and techniques for performing stem cell transplantations are changing. These changed practices will require new strategies for management and will present the clinician with new challenges.

Systemic fungal infections are becoming increasingly common in patients with haematological malignancies receiving anti-neoplastic therapy. The presence of acute myeloid or acute lymphoid leukaemia, plus the use of chemotherapy to totally ablate malignant bone marrow cells, puts patients in a protracted neutropenic state. During this profound and prolonged neutropenic phase, patients receive antibiotic therapy for suspected or identified bacterial infections. However, when fever or other signs of infection continue despite antibiotic therapy, patients frequently need to be treated for suspected or confirmed systemic fungal infections. These infections may occur in patients receiving either standard anti-leukaemia therapy or research protocol therapy involving new drugs, new drug combinations, higher doses, or newer schedules of established drugs. After antifungal therapy is initiated, it may be continued after discharge in outpatient or homecare settings.

Invasive aspergillosis (IA) is the most prevalent mould infection. This is illustrated by a number of surveillance studies. For example, an epidemiological surveillance network was set up in 18 teaching hospitals in Paris and the Greater Paris area.[9] Prospective surveillance was conducted between 1994 and 1999. Between 1994

and 1997, cases were categorized as proven or probable aspergillosis and then the European Organization for Research and Treatment of Cancer/Mycoses Study Group criteria were used.[21] The authors analysed 621 cases (115 proven, 506 probable). No seasonal variation was found. Haematological disorders (73%) including stem cell transplantation (36%), solid organ transplants (10%) and AIDS (9%) were the main underlying conditions. The crude mortality was 63%. Incidence of IA was 8% (95%CI: 6.5–9.5) in acute myelocytic leukaemia and 6.3% (95%CI: 4.3–8.3) in acute lymphocytic leukaemia. Incidence was 12.8% (95%CI: 10.8–14.8) following allogeneic stem-cell transplantation and 1.1% (95%CI: 0.7–1.5) following autologous stem cell transplantation (Table 1). This large series confirmed that patients with haematological disorders and transplants are the most at risk for IA.

Classically, the period of neutropenia caused by the conditioning regimen has been regarded as the most important period for systemic fungal infection. During the last few years, however, an increasing number of patients have been treated with reduced intensity conditioning regimens resulting in a shorter period of neutropenia. In contrast, the use of reduced intensity conditioning regimens will allow a larger patient population eligible for transplantation, including patients with previously documented invasive fungal infections. Furthermore, it has been recognized that aspects of the immune system other than granulocytes are very important for protection against invasive fungal infections. T cells probably have a very important role in host defence against mould infections, in particular aspergillosis. This is emphasized in a number of surveys showing that two-thirds of the cases of invasive aspergillosis occurred later than day 40 after transplantation and highlighting the recognized association between aspergillosis and acute graft-versus-host disease and its treatment. Since the risk of graft-versus-host disease is similar in patients undergoing myeloablative and reduced intensity conditioning regimens, the risks for late-occurring invasive fungal infections, in particular those caused by moulds, are similar in the two patient populations.

In parallel with the development of reduced conditioning regimens, the use of alternative donors for stem cell transplantation is increasing. These patients have a delayed T cell reconstitution and thereby are at particular risk for systemic fungal infection.

Table 1. Incidence of invasive aspergillosis in transplant recipients (data from Ref. 9)

Transplant type	Incidence (%) [no. cases/ no. recipients]	Study period
Allogeneic stem cell	12.8 [150/1175]	1995–1999
Autologous stem cell	1.1 [24/2115]	1995–1999
Bone marrow stem cell	6 [3/50]	1998–1999
Peripheral stem cell	1.6 [13/810]	1998–1999
Heart–lung	11.1 [2/18]	1996–1999
Small bowel/ liver–small bowel	10.7 [3/28]	1996–1999
Lung	2 [2/102]	1996–1999
Liver	1.9 [25/1298]	1995–1999
Heart	1.3 [6/451]	1995–1999
Kidney	0.4 [8/1930]	1995–1999
Kidney–pancreas	0 [0/86]	1995–1999

Non-myeloablative allogeneic transplantation is an emerging therapy for haematological and solid malignancies and potentially offers patients reduced transplant-related toxicity. Data regarding infectious complications of these protocols are limited, but early studies have demonstrated high rates of systemic fungal infection. The following case series illustrates this point.[19] Thirty-one consecutive cases of non-myeloablative transplantation were reviewed over a 2.5 year period, with a specific focus on infectious complications. Twenty-six patients (84%) had at least one significant infection during the year after transplantation, and infection-related mortality was 37%. Cytomegalovirus end-organ disease was diagnosed in three patients (10%). Ten patients (32%) were given the diagnosis of invasive fungal infection; 7 (23%) met criteria for proven systemic fungal infection. Fungal-related mortality was 80% within the group of patients with systemic fungal infection and accounted for a significant portion of the overall mortality in the study. Severe graft-versus-host disease, high-dose corticosteroid use, recurrent neutropenia, and relapsed or refractory disease were factors associated with development of systemic fungal infection.

The outcome of invasive aspergillosis remains poor. In many reviews of cases, the case fatality rates for cerebral, pulmonary, and sinus infections were found to be between 66 and 99%.[22] Little improvement has been achieved since 1995: disseminated or central nervous system disease still carries a case fatality rate higher than 85%, whereas diffuse pulmonary disease and sinus disease have case fatality rates of 60 and 26%, respectively. In a number of case series, the 1 year survival rate of persons with invasive aspergillosis was around 7%, and among all patients with invasive mould infections it was 20%.[22]

Within the past decade, infections due to infrequently encountered fungi (e.g. hyaline moulds, dematiaceous filamentous fungi, and zygomycetes) have become increasingly common in haematopoietic stem cell transplant recipients.[20,23] These trends are worrisome, given that opportunistic moulds are often refractory to conventional antifungal agents. Innate resistance or erratic susceptibility to amphotericin B is characteristic of certain fungi (e.g. *A. terreus, Scedosporium apiospermum,* and *Scedosporium prolificans*). The advent of novel antifungal agents represents an advance in the management of invasive mycoses. However, fungi such as *S. prolificans* and the zygomycetes are also resistant to the currently available triazoles and the echinocandins.

Changing patterns in fungal pneumonia in the immunocompromised patient

Pulmonary infections caused by fungi are among the commonest causes of mortality in the immunocompromised patient.[1,2] Two patterns are seen. Opportunistic infections with organisms such as *Aspergillus, Candida, Cryptococcus* and *Mucoraceae* are more commonly seen in neutropenic patients, and reactivation of indolent infection with *Histoplasma capsulatum, Coccidioides immitis* and *Blastomyces dermatitidis* commonly affects the patient with compromised cellular immunity.

Aspergillus pneumonia is mostly acquired nosocomially, with an overall incidence estimated at 4–13% in BMT patients, and up to 24% in heart transplant patients. However, data provided by PCR analysis of lower respiratory tract secretions before bone marrow transplantation suggests that patients are colonized with *Aspergillus* conidia prior to admission to hospital.[24] Moreover, more recent

data illustrate a shift toward a later occurrence of post-transplant IA, suggesting a need for close, prolonged surveillance in the outpatient environment.[25] Risk factors include prolonged neutropenia, antibiotic therapy, steroids, graft-versus-host disease, and T cell depletion of harvested marrow in the BMT patient. Increasingly, more cases are being seen at time points many months post-transplant suggesting community acquisition. Mortality has remained high, especially with dissemination (50–60% in neutropenia, 90% in BMT patients) despite new treatment options. One year survival in BMT patients with invasive aspergillosis is still less than 10%. Developments in diagnosis have allowed targeted therapy in some cases. Serial high-resolution computed tomography (HRCT) scanning visualizes a number of manifestations of pulmonary aspergillosis including the halo sign. This can be seen in 70–90% of cases and allows for earlier therapy. Various non-culture diagnostic markers now contribute to diagnosis and institution of earlier, targeted therapy.[26]

Emerging fungal pathogens in solid organ transplant patients

Invasive aspergillosis is the major source of morbidity among solid organ transplant recipients.[4,5,22,27,28] Between 3.3% and 16% of lung transplant recipients develop this disease. In addition to lung transplants, recipients of liver transplants are also at increased risk of developing invasive aspergillosis. Despite documenting improving technical developments in the liver transplant process, one large US transplant centre experienced rates of invasive aspergillosis between 1990 and 2000 that ranged from 1.6% to 7.6%.[5] Liver transplant recipients are also uniquely predisposed to dissemination of infection beyond the lungs, which occurs in ~50–60% of cases.[22] This disease can also occur in low-risk groups, such as renal transplant recipients. Here, invasive aspergillosis has been reported in ~0.7% and in up to 4% of patients.[22] Despite a relatively lower overall incidence compared with other organ transplant recipients, invasive aspergillosis is a significant contributor to morbidity in renal transplant recipients. An outbreak of aspergillosis was recently reported among renal transplant recipients following the use of a new combination of immunosuppressive drugs (mycophenolate and sirolimus), suggesting that these patients may also be at increased risk during periods of severe immunosuppression.[29]

The emergence of filamentous fungi other than *Aspergillus* in solid organ transplant patients is also being recognized.[5,30] In one centre, 53 liver and heart transplant recipients with invasive mycelial infections were prospectively identified in a multicentre study. Invasive mycelial infections were due to *Aspergillus* species in 69.8% of patients, to non-*Aspergillus* hyalohyphomycetes in 9.4%, to phaeohyphomycetes in 9.4%, to zygomycetes in 5.7%, and to other causes in 5.7%. Infections due to mycelial fungi other than *Aspergillus* species were significantly more likely to be associated with disseminated ($P = 0.005$) and central nervous system ($P = 0.07$) infection than were those due to *Aspergillus* species. Overall mortality at 90 days was 54.7%. The associated mortality rate was 100% for zygomycosis, 80% for non-*Aspergillus* hyalohyphomycosis, 54% for aspergillosis, and 20% for phaeohyphomycosis.

A recent review of the literature has focused on the risk factors predisposing to systemic fungal infection in solid organ transplant patients.[5] An English language literature search (MEDLINE 1990–2000) and bibliographic review of textbooks and review articles was undertaken. Twenty-three articles were selected from the literature. It was found that fungal infections in organ transplant patients were generally divided into two types: (i) disseminated primary or reactivation infection with one of the geographically restricted systemic mycoses; (ii) opportunistic infection by fungal species that rarely cause invasive infection in normal hosts. The review emphasizes that the risk factors of fungal infection after a transplant should be evaluated and predicted according to the organ recipient's conditions before, during and after the transplant.

Changing patterns in antifungal resistance

The first reports of antifungal resistance occurred in patients with mucocutaneous candidosis treated with ketoconazole, but since the AIDS epidemic began, this problem has gained great clinical relevance.[31] The typical background for the development of azole resistance is the prolonged and repeated use of fluconazole for the management of oral and oesophageal candidosis in AIDS patients with low CD4+ cell counts, and use as prophylaxis. Patients initially infected by susceptible strains of *C. albicans* subsequently developed infection by the same genotype of *C. albicans*, but with high MICs. Another pattern of resistance is the acquisition of infection caused by azole-resistant non-*albicans* species, such as *C. krusei* and *C. glabrata*. However, during the late 1990s, the introduction of HAART exerted a tremendous impact on the natural history of HIV infection and its complications. Indeed, the incidence of opportunistic infections, including oropharyngeal candidosis due to resistant strains has decreased significantly.

Outside the setting of oropharyngeal candidosis in AIDS patients, reports of infection by resistant strains have become more frequent. With the widespread use of azoles, especially fluconazole, for prophylaxis in neutropenic cancer patients, this problem has gained increased significance. A phenomenon that has been increasingly reported among patients receiving fluconazole is the shift from highly susceptible to less susceptible species of *Candida*. Epidemiological studies performed in patients with cancer and fungaemia have shown that while the number of cases caused by *C. albicans* has decreased, the frequency of infection due to *C. krusei* and *C. glabrata* has increased substantially. While *C. krusei* is considered resistant to fluconazole, the MIC values of fluconazole for the *C. glabrata* isolates are variable, but are much higher than those reported for C. *albicans*, *C. tropicalis* and *C. parapsilosis*.

This increase in the incidence of infection due to less-susceptible *Candida* species has been attributed to the widespread use of fluconazole. For instance, in large prospective surveys conducted in European institutions, antifungal prophylaxis was a strong predictor for non-*albicans* candidaemia. The influence of fluconazole use on the development of azole resistance has also been seen in bone marrow transplant recipients.

The development of candidaemia during antifungal treatment (breakthrough candidaemia) is another phenomenon that may be due to the emergence of resistant strains. During the past decade, reports of the occurrence of breakthrough candidaemia have been published. Unfortunately, in the majority of such reports, no information on the MICs was provided. However, it seems that in most cases, breakthrough candidaemia is not related to the development of infection by resistant strains.

In summary, during the past decade, fluconazole has been extensively used in neutropenic patients. This has resulted in a

marked decrease in the incidence of invasive candidosis, especially in allogeneic bone marrow transplants. However, this was accompanied by a shift from highly susceptible to less susceptible *Candida* species, by a process of selection. Indeed, *C. glabrata* has emerged as an important pathogen, causing fungaemia in many countries. In addition, resistance has also emerged as a result of the acquisition of resistance in otherwise susceptible *Candida* species, but at a much smaller magnitude. Finally, the limitations of the present methods for assessing antifungal susceptibility hamper any conclusion about resistance to amphotericin B and preclude their use for therapy guidance in the clinical setting.

Transparency declaration

M. D. R. has received fees for speaking at symposia organized on behalf of Janssen-Cilag/Ortho-Biotech and is a member of the Janssen-Cilag/Ortho-Biotech advisory board for itraconazole.

References

1. Richardson MD, Warnock DW. *Fungal Infection: Diagnosis and Management,* 3rd edn. Oxford: Blackwell Publishing, 2003.

2. Clark TA, Hajjeh RA. Recent trends in the epidemiology of invasive mycoses. *Curr Opin Infect Dis* 2002; **15**: 569–74.

3. Maertens J, Vrebos M, Boogaerts M. Assessing risk factors for systemic fungal infections. *Eur J Cancer Care* 2001; **10**: 56–62.

4. Patterson JE. Epidemiology of fungal infections in solid organ transplant patients. *Transplant Infect Dis* 1999; **1**: 229–36.

5. Singh N. Fungal infections in the recipients of solid organ transplantation. *Infect Dis Clin N Am* 2003; **17**: 113–34.

6. Eggimann P, Garbino J, Pittet D. Epidemiology of *Candida* species infections in critically ill non-immunosuppressed patients. *Lancet Infect Dis* 2003; **3**: 685–702.

7. Hobson RP. The global epidemiology of invasive *Candida* infections—is the tide turning? *J Hosp Infect* 2003; **55**: 159–68.

8. Garbino J, Kolarova L, Rohner P *et al*. Secular trends of candidemia over 12 years in adult patients at a tertiary care hospital. *Medicine (Balt)* 2002; **81**: 425–33.

9. Cornet M, Fleury L, Maslo C *et al*. Epidemiology of invasive aspergillosis in France: a six-year multicentric survey in the Greater Paris area. *J Hosp Infect* 2002; **51**: 288–96.

10. Lortholary O, Denning DW, Dupont DW. Endemic mycoses: a treatment update. *J Antimicrob Chemother* 1999; **43**: 321–31.

11. Chapman RL. Candida infections in the neonate. *Curr Opin Pediatr* 2003; **15**: 97–102.

12. Vanden Bergh MFQ, Verweij PE, Voss A. Epidemiology of nosocomial fungal infections: invasive aspergillosis and the environment. *Diagn Microbiol Infect Dis* 1999; **34**: 221–7.

13. Munoz P, Burillo A, Bouza E. Environmental surveillance and other control measures in the prevention of nosocomial fungal infections. *Clin Microbiol Infect* 2001; **7** Suppl 2: 38–45.

14. Gudlaugsson OG, Gillespie S, Lee K *et al*. Attributable mortality of nosocomial candidemia, revisited. *Clin Infect Dis* 2003; **37**: 1172–7.

15. Kibbler CC, Seaton S, Barnes RA *et al*. Management and outcome of bloodstream infections due to *Candida* species in England and Wales. *J Hosp Infect* 2003; **54**: 18–24.

16. de Irala-Estévez J, Martinez-Concha D, Diaz-Molina C *et al*. Comparison of different methodological approaches to identify risk factors of nosocomial infection in intensive care units. *Intensive Care Med* 2001; **27**: 1254–62.

17. Pittet D, Monod M, Suter PM *et al*. *Candida* colonization and subsequent infections in critically surgical patients. *Ann Surg* 1994; **220**: 751–8.

18. Mullen CA, Abd El-Baki H, Samir H *et al*. Non-*albicans Candida* is the most common cause of candidemia in pediatric cancer patients. *Support Care Cancer* 2003; **11**: 321–5.

19. Hagen EA, Stern H, Porter D *et al*. High rate of invasive fungal infections following non-myeloablative allogeneic transplantation. *Clin Infect Dis* 2003; **36**: 9–15.

20. Pagano L, Girmenia C, Mele L *et al*. Infections caused by filamentous fungi in patients with hematologic malignancies. A report of 391 cases by GIMEMA infection program. *Haematologia* 2001; **86**: 862–70.

21. Ascioglu S, Rex JH, de Pauw B *et al*. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis* 2002; **34**: 7–14.

22. Singh N, Paterson DL. *Aspergillus* infections in transplant patients. *Clin Microbiol Rev* 2005; **18**: 44–69.

23. Marr KA, Carter RA, Crippa F *et al*. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2002; **34**: 909–17.

24. Einsele H, Quabeck K, Muller KD *et al*. Prediction of invasive pulmonary aspergillosis from colonization of lower respiratory tract before bone marrow transplantation. *Lancet* 1998; **352**: 1443.

25. Grow WB, Moreb JS, Roque D *et al*. Late onset of invasive aspergillus infection in bone marrow transplant recipients at a university hospital. *Bone Marrow Transplant* 2002; **29**: 15–9.

26. Jones BL, McLintock LA. Impact of diagnostic markers on early antifungal therapy. *Curr Opin Infect Dis* 2003; **16**: 521–6.

27. Montoya JG, Chaparro SV, Celis D *et al*. Invasive aspergillosis in the setting of cardiac transplantation. *Clin Infect Dis* 2003; **37** Suppl 3: S281–92.

28. Minari A, Husni R, Avery RK *et al*. The incidence of invasive aspergillosis among solid organ transplant recipients and implications for prophylaxis in lung transplants. *Transplant Infect Dis* 2002; **4**: 195–200.

29. Panackal AA, Dahlman A, Keil KT *et al*. Outbreak of invasive aspergillosis among renal transplant recipients. *Transplantation* 2003; **75**: 1050–3.

30. Husain S, Alexander BD, Munoz P *et al*. Opportunistic mycelial fungal infections in organ transplant recipients: emerging importance of non-*Aspergillus* mycelial fungi. *Clin Infect Dis* 2003; **37**: 221–9.

31. Perea S, Patterson TF. Antifungal resistance in pathogenic fungi. *Clin Infect Dis* 2002; **35**: 1073–80.